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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,728	05/19/2005	Kjell Eriksson	PU0297	7779

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
07/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,728	ERIKSSON ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice to comply, sequence rules.

DETAILED ACTION

Requirement to comply with sequence rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, the specification on pages 15 and 16 contains nucleotide sequences that lack a sequence identifier.

Any response to this action must comply with the sequence rules, this requirement will not be held in abeyance.

Claim Objections

Claim 2 is objected to because of the following informalities: this claim recites that the biological solution results from a synthesis of antisense oligonucleotides. Since a synthesis reaction, particularly an automated synthesis reaction, would not be readily recognized as resulting in a biological solution, it is recommended this claim be amended to recite that the biological solution is a synthesis reaction of antisense oligonucleotides. Appropriate correction is required.

Claim 3 is objected to because of the following informalities: this claim recites that fully thioated oligonucleotides are separated from "incorrectly synthesized" oligonucleotides. This claim depends from claim 1, which recites only that fully thioated oligonucleotides are separated from incorrectly thioated oligonucleotides, defined in the specification as having less than all positions thioated. Based on the description of incorrectly synthesized oligonucleotides at page 10 of the specification, this claim appears to recite that full-length sequences are separated from shorter sequences that may nevertheless be "fully thioated". Amending the claims to clarify that the method is intended to encompass the embodiments of claim 3 as well as the embodiments of claim 4 would be remedial. Appropriate correction is required.

Claim Rejections - 35 USC § 101 & § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 provides for the use of an immobilised metal ion adsorption chromatography resin, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 9 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for separation of fully thioated antisense oligonucleotides from incorrectly thioated or incorrectly synthesized oligonucleotides using Fe^{3+} or Zr^{2+} IMAC resins and the buffer conditions described in the working examples, does not reasonably provide enablement for use of any metal ion and any eluent conditions to separate fully thioated antisense oligonucleotides from incorrectly thioated or incorrectly synthesized oligonucleotides. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The claims are directed to methods of isolating fully thioated single stranded oligonucleotides from a solution, comprising adsorbing the oligonucleotides to an immobilized metal ion adsorption chromatography (IMAC) resin and contacting the resin with an eluent under conditions that provide desorption of the oligonucleotides and separate fully thioated antisense oligonucleotides from incorrectly thioated oligonucleotides. In specific embodiments the solution comprises a synthesis reaction, the fully thioated oligonucleotides are separated from oligonucleotides of different length, the metal ion is Zr^{2+} or Fe^{3+}, the pH of the solution is below 7, and the isolated oligonucleotides are further polished. The claims encompass the use of any IMAC resin to separate thioated oligonucleotides under any conditions sufficient to provide the desired separation.

The specification describes IMAC as a chromatographic purification method based on the interactions between a target compound and metal chelating groups

present on a stationary phase. The specification contemplates that suitable coordinating ions useful in the instant invention include Cu(II), Zn(II), Ni(II), Ca(II), Co(II), Mg(II), Fe(III), Al(III), Ga(III), and Sc(III). The working examples describe the use of Fe^{3+} and Zr^{2+} IMAC resins to separate phosphorothioate oligonucleotides from oligonucleotides with different numbers of phosphodiester linkages.

The claims recite that the oligonucleotides are eluted from the column under conditions that provide desorption of the oligonucleotide from the resin. The specification contemplates at page 12 that elution of the desired antisense oligonucleotides from the resin can be performed according to standard methods using an increasing pH and/or phosphate gradient, and notes that the skilled person can easily set the appropriate conditions for elution. However, in both examples 1 and 3 it is stated that the solvents/buffer used are "rather unusual" for IMAC, with a solution of 0.1% acetic acid in water used as binding "buffer" in example 1 and 15 mM sodium acetate and pH 5.0 binding buffer used in example 3. The specification further notes that neither the binding nor the elution conditions were optimized.

The prior art teaches that internucleoside linkages are of little consequence in the interactions of nucleic acids with IMAC resins. For example, Hubert et al. (Journal of Chromatography 1980) investigated chelating resins comprising copper ions and teach that nucleosides, nucleotides and dinucleotides are all retained but conclude (see pages 253-254) the interaction of nucleotides with immobilized copper resins proceeds mainly via the heterocyclic bases.

The teachings of Willson et al. (WO 02/46398, cited on IDS) are similar. Willson et al. teach that IMAC has potential for purification of nucleic acids but again teaches that the interaction of the nucleic acid with the IMAC resin is through the nucleobase components. Willson et al. specifically disclose (see paragraphs 182 and 193) that binding of nucleic acids to Ni(II) IMAC resins does not occur through ribose or phosphodiester backbone interactions.

Dobrowolska et al. (Journal of Chromatography 1991) teach (see the abstract) that cyclic mononucleotides and dinucleotides containing only internal phosphate groups are not retained on a Fe^{3+} column while mononucleotides are retained. Dobrowolska et al. conclude that interaction of nucleotides with a Fe-based IMAC resin requires a free terminal phosphate.

Based on the teachings of the prior art, the skilled artisan would not recognize that phosphorothioate nucleic acids could be separated from non-phosphorothioate oligonucleotides using metal ion adsorption chromatography. In order to predictably use the claimed invention throughout its full scope the skilled artisan cannot rely on knowledge found in the prior art and must depend only on the disclosure found in the instant specification for guidance with regard to suitable metal ions and elution conditions. While the instant specification provides examples of successful separation of oligonucleotides with Fe^{3+} and Zr^{2+} that are counter to the teachings of the art, in view of the unexpected success demonstrated in the specification for Fe- and Zr-containing resins, the skilled artisan would not know what other metal ions can be used to separate fully thioated antisense oligonucleotides. The unpredictability is compounded by the

elution conditions used in the working examples, which applicants themselves characterize as "rather unusual" for IMAC. If only "unusual" elution conditions work, (which in itself remains to be experimentally determined), the skilled artisan has no guidance that would lead to the specific "unusual" elution conditions needed to successfully use the claimed invention on IMAC resins comprising metal ions other than Fe^{3+} and Zr^{2+}.

Before performing the invention throughout its full scope, the skilled artisan armed only with the instant specification, would have to perform trial and error experimentation with metal ions and elution conditions to determine the proper combination of metal ions and "unusual" elution conditions. Therefore, the skilled artisan would not know how to use the invention for other metal ions or with other elution conditions without undue experimentation and claims 1-8 are not enabled.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

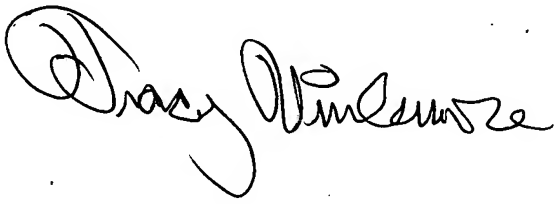
Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now

contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
May 1, 2007



NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing".

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Pages 15 and 16 of the specification lack sequence identifiers.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing". (If the unidentified sequences are not provided on the CRF)

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification. (If the unidentified sequences are not provided in the paper copy)

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). (If a new paper and/or CRF are required)

For questions regarding compliance to these requirements, please contact:

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